specifically using at least one ligand. The term "ligand" is intended to mean in particular a monoclonal or polyclonal antibody, or a fragment of said antibodies, preferably a monoclonal antibody. The monoclonal antibodies directed against a Vβ of interest are produced by conventional techniques used to produce antibodies against surface antigens. Mice or rabbits are immunized (i) either with a natural or recombinant protein, (ii) with an immunogenic peptide, (iii) or with murine cells which express the protein or the peptide of interest and MHCII molecules. The Balb/c murine line is the most commonly used. The immunogen may also be a peptide chosen from the peptides defined from the primary sequences of the Vβs of interest. The proteins or peptides are coupled to keyhole limpet hemocyanin (peptide-KLH), as a support for their use in immunization, or coupled to human serum albumin (peptide-HSA). The animals are given an injection of peptide-KLH or of peptide-HSA, using complete Freund's adjuvant (IFA). The sera and the hybridoma culture supernatants derived from the animals immunized with each peptide are analyzed for the presence of antibodies with an ELISA assay using the initial molecules. The spleen cells of these mice are recovered and fused with myeloma cells. Polyethylene glycol (PEG) is the most commonly used fusion agent. The hybridomas producing the most specific and the most sensitive antibodies are selected. The monoclonal antibodies can be produced *in vitro* by cell culture of the hybridomas produced or by recovering murine ascites fluid after intraperitoneal injection of the hybridomas into mice. Whatever the method of production as supernatant or as ascites, it is then important to purify the monoclonal antibody. The purification methods used are essentially filtration over ion exchange gel or by exclusion chromatography, or even immunoprecipitation. For each antibody, the method which will make it possible to obtain the best yield should be chosen. A sufficient number of antibodies is screened in functional assays in order to identify the antibodies which are the most effective in binding the molecule of interest and/or in blocking the activity of the molecule of interest. The selected monoclonal antibodies are humanized using standard "CDR grafting" methods

(protocol carried out by many companies, in the form of a service). These humanized antibodies can be tested clinically in patients. The effectiveness of these antibodies can be monitored using clinical parameters. The *in vitro* production of antibodies, of antibody fragments or of antibody derivatives, such as chimeric antibodies which may or may not be humanized and which are produced by genetic engineering, in eukaryotic cells has been described (EP 120 694 or EP 125 023) and can also be applied to the present invention;

Page 19, line 35- page 20, line 29, delete current paragraphs and insert therefor:

In order to evaluate the effectiveness of the molecules for therapeutic use, i.e. one or more molecule(s) capable of inhibiting the expansion or the loss of the T lymphocytes of a given Vβ,

(i) blood mononucleated cells are sampled, said cells originating from patients suffering from an autoimmune disease or suspected or having a risk of developing the disease, in particular MS, and from healthy individuals,

(ii) said blood mononucleated cells originating from MS patients or from healthy individuals are brought into contact with culture supernatants, or a fraction of culture supernatant, of cells chosen from blood mononucleated cells, choroid plexus cells, leptomeningeal cells and cells derived from established cell lines, such as the cells of the PLI-2 cell line and the LM7PC cell line, and

(iii) the inhibition of said expansion and, optionally, co-expansion, or the inhibition of said loss and, optionally, co-decrease, of the lymphocytes bearing at least one determinant chosen from Vβ16, Vβ2, Vβ3, Vβ7, Vβ8, Vβ12, Vβ14, Vβ17 and Vβ22, in particular Vβ16 and/or Vβ17, Vβ16, Vβ3 and Vβ12 or Vβ16, Vβ7, Vβ14 and Vβ17, particularly Vβ16, Vβ7 and Vβ17, using the blood mononucleated cells of step (i), in the presence of said molecule at given doses, are detected using a ligand as described above or amplification combined with electrophoresis as described above.

Page 29, lines 28-34, delete current paragraph and insert therefor:

a3

On the basis of the amino acid sequence of the molecules of interest of the invention, peptide sequences of these molecules or fragments of peptides sequences of these molecules, corresponding to all or part of the primary sequence of these molecules, can be synthesized using conventional methods of peptide synthesis or obtained by genetic recombination.

Page 33, line 3- page 34, line 35, delete current paragraphs and insert therefor:

a4

The *in vitro* production of antibodies, of antibody fragments or of antibody derivatives, such as chimeric antibodies which may or may not be humanized and which are produced by genetic engineering, in eukaryotic cells has been described (EP 120 694 or EP 125 023) and can also be applied to the present invention,

- at least one molecule which inhibits the function of at least one molecule chosen from the molecules of interest of the invention or the fragments thereof,

- at least one molecule which regulates the expression of at least one molecule chosen from the molecules of interest of the invention or the fragments thereof, for example to block the transcription or the translation of these molecules,

- at least one molecule which regulates the metabolism of at least one protein chosen from the molecules of interest of the invention or the fragments thereof,

- at least one molecule which regulates the expression and/or the metabolism of a ligand for at least one protein chosen from the molecules of interest of the invention or the fragments thereof, for example a receptor or a cofactor,

- at least one nucleic acid sequence comprising at least one gene of therapeutic interest, the nucleic acid sequence of which is deduced from the DNA and RNA sequences encoding all or part of the molecules of interest of the invention, in combination with elements which ensure the expression of said gene of therapeutic interest *in vivo* in target cells intended to be genetically modified with the nucleic acid sequence of the gene of therapeutic interest. The

Cont A4

genes may or may not be mutated. They may also consist of nucleic acids modified such that it is not possible for them to integrate into the genome of the target cell, or of nucleic acids stabilized using agents such as spermine. Such a gene of therapeutic interest in particular encodes:

- at least a protein chosen from the molecules of interest identified in the present invention or the fragments thereof, and/or

- at least a ligand or any part of a ligand capable of attaching to at least one protein or one protein fragment chosen from the molecules of interest identified in the present invention or the fragments thereof, which may or may not inhibit the function of the molecule of interest, and/or

- at least all or part of a polyclonal or monoclonal antibody capable of attaching to at least one protein or one protein fragment chosen from the molecules of interest identified in the present invention or the fragments thereof, which may or may not inhibit the function of the molecule of interest. It may in particular be a native transmembrane antibody, or a fragment or derivative of such an antibody, provided that said antibody, antibody fragment or antibody derivative is expressed at the surface of the genetically modified mammalian target cell and is capable of binding to a polypeptide present at the surface of a cytotoxic effector cell or of a helper T lymphocyte involved in the process of activation of such a cell, and/or

- at least a molecule which inhibits at least one protein or the fragments thereof, said protein being chosen from the molecules of interest identified in the present invention, which can inhibit the function and/or the metabolism and/or the binding of the molecules of interest or of the fragments thereof.

Page 35, line 26- page 36, line 16, delete current paragraph and insert therefor:

A5

The nucleic acid sequence is preferably a DNA or RNA sequence which is naked, i.e. free of any compound which facilitates its introduction into cells (nucleic acid sequence

transfer). However, according to a second embodiment of the invention, in order to promote its introduction into target cells and in order to obtain the genetically modified cells of the invention, this nucleic acid sequence may be in the form of a "vector", and more particularly in the form of a viral vector, such as for example an adenoviral vector, a retroviral vector or a vector derived from a poxvirus, in particular derived from the vaccinia virus or from the Modified Virus Ankara (MVA), or of a nonviral vector, such as for example a vector consisting of at least one said nucleic acid sequence complexed with or conjugated to at least one carrier molecule or substance selected from the group consisting of a cationic amphiphile, in particular a cationic lipid, a cationic or neutral polymer, a polar proctic compound, in particular chosen from propylene glycol, polyethylene glycol, glycerol, ethanol, 1-methyl-L-2-pyrrolidone, or derivatives thereof, and a polar aprotic compound, in particular chosen from dimethyl sulfoxide (DMSO), diethyl sulfoxide, di-n-propyl sulfoxide, dimethylsulfone, sulfolane, dimethylformamide, dimethylacetamide, tetramethylurea, acetonitrile, or derivatives thereof. The literature provides a considerable number of examples of such viral and nonviral vectors.

Page 39, line 1- page 40, line 6, delete current paragraphs and insert therefor:

These nucleic acid sequences and/or vectors make it possible to target the cells in which the protein or the protein fragment is expressed, either using a targeting molecule introduced onto the vector or using a particular property of the cell;

- at least one mammalian cell which does not naturally produce at least one molecule of interest of the invention or any fragment of these molecules, or antibodies specific for at least one of said molecules of interest of the invention or of the fragments thereof, said mammalian cell being genetically modified *in vitro* with at least one nucleic acid sequence or a fragment of a nucleic acid sequence or a combination of nucleic acid sequences corresponding to nucleic acid fragments derived from the same gene or from different genes, said nucleic acid sequence(s) being deduced from the DNA and RNA sequences encoding the molecules of

Cont a6

interest of the invention or any fragment, said gene of therapeutic interest encoding all or part of the molecule of interest of the invention, of a fragment of the molecule or of an antibody specific for the molecule which will be expressed at the surface of said mammalian cell (Toes et al., 1997, PNAS 94: 14660-14665). Thus, said cell contains at least one gene which encodes *in vivo*:

- at least one protein chosen from the molecules of interest of the invention and/or the fragments thereof, and/or

- at least one peptide defined on the basis of the primary sequence of at least one protein chosen from the molecules of interest of the invention and/or the fragments thereof, and/or

- at least any molecule which inhibits the activity and/or the binding and/or the expression of these molecules, and/or

- at least one peptide derived from the primary sequence of a protein chosen from the molecules of interest of the invention and/or the fragments thereof, and capable of binding to at least one MHCI and/or MHCII glycoprotein, and/or

- at least one ligand and/or any antibody and/or any part of an antibody capable of binding to at least one protein chosen from the molecules of interest of the invention and/or the fragments.

Page 40, lines 17-30, delete current paragraph and insert therefor:

a7

The invention also relates to the modified cells and a method for preparing a cell as described above, characterized in that at least one nucleic acid sequence containing at least one gene of therapeutic interest and elements which ensure the expression of said gene in said cell are introduced into a mammalian cell by any suitable means, said gene of therapeutic interest containing a nucleic acid sequence encoding a molecule or a molecule fragment *in vivo*, as described just above. More particularly, it relates to prokaryotic cells, yeast cells and animal

Cont a1

cells, in particular mammalian cells, transformed with at least one nucleotide sequence and/or one vector as described above.

Page 45, lines 2-35, delete current paragraph and insert therefor:

a8

In particular, the therapeutic and/or prophylactic agent is chosen from DNA and/or RNA molecules; antisense oligonucleotides and anti-gene oligonucleotides; at least one ligand capable of interacting with Vβ16 and/or Vβ17, in particular Vβ16, optionally in combination with at least one ligand capable of interacting with at least one of Vβ2, Vβ3, Vβ7, Vβ8, Vβ12, Vβ14, Vβ17 and Vβ22, and preferentially Vβ3 and Vβ12; from antibodies, preferably monoclonal antibodies and anti-receptors for the TCRs of the various Vβs above; at least one ligand capable of interacting with Vβ16 and/or Vβ17, optionally in combination with at least one ligand capable of interacting with at least one of Vβ7, Vβ14, Vβ17 and Vβ22, and preferentially Vβ7 and Vβ17, in particular antibodies, and preferably monoclonal antibodies, or fragments of said antibodies and anti-receptors for the TCRs of the various Vβs above; an agent capable of blocking the interaction of the superantigen with the antigen-presenting cells; at least one cell, preferably a cell of mammalian origin, genetically modified *in vitro* with a therapeutic agent which consists of at least one nucleic acid molecule encoding at least one molecule, the protein sequence of which corresponds to the sequence encoding the molecules as defined above, in particular a DNA and/or RNA molecule; at least one cell, preferably a cell of mammalian origin, genetically modified *in vitro* with a therapeutic agent which consists of at least one nucleic acid molecule encoding at least one ligand as defined above, in particular a DNA and/or RNA molecule.

Page 46, lines 7-28, delete current paragraph and insert therefor:

a9

In particular, the therapeutic and/or prophylactic agent is chosen from DNA and/or RNA molecules; antisense oligonucleotides and anti-gene oligonucleotides; at least one ligand capable of interacting with MSRV-1 proteins, in particular the env protein of MSRV-1, from antibodies,

preferably monoclonal antibodies and anti-MSRV-1 proteins, in particular anti-env proteins of MSRV-1; at least one cell, preferably a cell of mammalian origin, genetically modified in vitro with a therapeutic agent which consists of at least one DNA molecule encoding at least one molecule, the protein sequence of which corresponds to the sequence encoding the molecules as defined above, in particular a DNA and/or RNA molecule; at least one cell, preferably a cell of mammalian origin, genetically modified in vitro with a therapeutic agent which consists of at least one DNA molecule encoding at least one ligand as defined above, in particular a DNA and/or RNA molecule.

Page 51, line 10- page 52, line 17, delete current paragraphs and insert therefor:

The invention relates to the *in vivo* expression of nucleotide sequences and/or of vectors as described above, i.e. sequences corresponding to genes of therapeutic interest, in particular:

- either at least encoding a protein chosen from the molecules of interest identified in the present invention or the fragments thereof; and/or

- at least encoding all or part of a polyclonal or monoclonal antibody capable of binding to at least one protein chosen from the molecules of interest identified in the present invention and the fragments thereof. It may be a native transmembrane antibody, or a fragment or derivative of such an antibody, provided that said antibody, antibody fragment or antibody derivative is expressed at the surface of the genetically modified mammalian target cell and that said antibody is capable of binding to a polypeptide present at the surface of a cytotoxic effector cell or of a helper T lymphocyte and inhibiting the activity of at least one molecule of interest of the invention. They may be antibody fragments expressed by cells capable of secreting said antibodies into the blood circulation of a mammal or patient carrying the cells genetically modified with the gene encoding the antibody; and/or

- at least encoding a molecule which inhibits at least one protein chosen from the molecules identified in the present invention or the fragments thereof; and/or

Ant A10

- at least encoding a ligand or any part of the ligand capable of binding to at least one protein chosen from the molecules of interest identified in the present invention or the fragments thereof, and/or of inhibiting its function. Using the amino acid sequences of the molecules of interest of the invention or of the fragments thereof, it is within the scope of those skilled in the art to deduce the DNA and RNA nucleotide sequences corresponding to the molecules of interest or to the fragments thereof, using the genetic code and taking into account the degeneracy thereof. Thus, the present invention relates to the use of these nucleotide sequences in the form of antisense sequences, of sequences encoding a therapeutic gene and of sequences which can be contained in a vector for performing cell transformation *ex vitro* and/or *in vivo* (gene therapy).

Page 55, lines 13-38, delete current paragraph and insert therefor:

A1

According to a particular embodiment, cytotoxic effector cells or helper T lymphocytes are genetically modified, in particular *in vivo*, so that they express, at their surface, ligands for at least one of said molecules of interest of the invention, which are not naturally expressed by these cells, and which are capable of binding to all or part of at least one of the molecules of interest of the invention at the surface of the same cell or of another cell, and of inhibiting the activity of at least one molecule of interest of the invention, by introducing into these cells nucleic acid sequences containing the gene encoding such a polypeptide. In accordance with the present invention, it is also possible to select a nucleic acid sequence containing a gene of therapeutic interest encoding all or part of an antibody directed against a protein chosen from the molecules of interest of the invention and the peptide sequences and/or the fragments of said sequences, which is capable of being expressed at the surface of the target cells of the patient to be treated, said antibody being capable of binding, via these effector cells, to a polypeptide of the molecules of interest of the invention present at the surface of the cytotoxic lymphocytes and/or helper T lymphocytes, or even of inhibiting the activity of these molecules of interest.

Page 63, lines 21-37, delete current paragraph and insert therefor:

Q12

Human lymphocytes are isolated from 50 ml of heparinized blood diluted 50/50 with RPMI 1640, by centrifugation on a Ficoll gradient. They are carefully harvested from the band, as are possible cellular aggregates which may float just above the band. The cells are then washed twice in RPMI 1640 medium. After these washes, the cells are resuspended at the concentration of 2×10^6 cells/ml in RPMI 1640 medium containing:

200 U/ml penicillin

20 mg/l streptomycin

6 mM L-glutamine

1% sodium pyruvate

1% essential amino acids

anti-leukocytic IFN antibody (polyclonal anti-alpha interferon sold by Sigma) added to 10 U/ml final.

Page 72, lines 3-8, delete current paragraph and insert therefor:

Q13

Two mixtures of antibodies were used to detect the presence of viral antigens in the human lymphocytes cultured in the presence of extracts of LES and GRE choroid plexus CS, under the same conditions as for the analysis of the expansion of the TCR (T-cell receptor) Vβ families.

Page 78, lines 4-12, delete current paragraph and insert therefor:

Q14

Example 12: Stimulation of cytokine production.

The cultures of lymphocytes stimulated with MSBL differ in that they produce significantly greater amounts of IL-6 and of γ-INF compared to those stimulated with CTBL. On the other hand, the TNF-α titers are very low and equivalent for the two types of culture. The results, expressed in pg/ml of culture corresponding to 2×10^6 cells, are shown in Table 5.